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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
SWOPE, SHERIDAN

ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/802,285	LIU ET AL.	
	Examiner	Art Unit	
	Sheridan L. Swope	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,18,20,23,27,28,32-36 and 50-60* is/are pending in the application.

4a) Of the above claim(s) *1-12,18,20, 36, and 50-60* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23,28 and 32-35* is/are rejected.

7)☒ Claim(s) *27* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 March 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4&5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's election with traverse of Invention I, Claims 23, 27, 28, and 32-35 in Paper No. 10 is acknowledged. The traversal is on the ground(s) that there would not be a serious burden on the examiner if restriction were not required. This is not found persuasive. Each invention with a unique classification requires an independent search; for example, Groups I and II. Although Groups III, VI, and VII have the same major classification, they are distinct as they encompass methods using distinct substrates and producing distinct products and, thus, would require separate searches. Groups IV and VIII are distinct chemical entities and would also require separate searches. Likewise, Groups V and IX use different products and would require different searches. The restriction requirement is still deemed proper and is therefore made FINAL.

Claims 1-12,18,20, 36, and 50-60 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected Inventions, there being no allowable generic or linking claim. Claims 23, 27, 28, and 32-35 are hereby examined.

Specification- Objections

The legends for Figs 8 and 13 are objected to for lack of clarity. The legend for Fig 8 fails to describe the use of heparinase III, inactive heparinase III, and PBS. Also for Fig 8, descriptions of the upper and lower panels should be included and said panels should be labeled a and b, respectively. Fig 13 is completely unclear and appears to have six panels. Correction of legends 8 and 13 as well as Fig 13 is required.

For Example 6, pages 62-67, sections b-f are presented but, not a section a. For Example 7, it is not clear why the methods are indicated as sections a-c. Appropriate corrections are required.

Oath/Declaration

The Declaration does not identify the dates of execution for the signatures of Ganesh Venkataraman and Ram Sasisekharan. New and dated signatures may be provided on a supplemental oath or declaration.

Claim Rejections - 35 USC § 112-Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 28 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 28 recites a substantially pure heparinase III comprising a polypeptide having mutations wherein at least one of His36, His105, His110, His139, His152, His225, His234, His241, His424, His469, or His539 of SEQ ID NO: 2 is substituted. However, SEQ ID NO: 2, which appears to be the sequence for heparinase I, does not have a histidine residue at either His36, His105, His110, His139, His152, His225, His234, His241, His424, His469, or His539. Therefore, Claim 28 is rejected under 35 U.S.C. 112, second paragraph for failing to distinctly claim the subject matter which applicant regards as the invention.

Examiner's note: for purposes of examination, it is assume that SEQ ID NO: 2 is meant to be the sequence presented in Su et al, 1997 (IDS), Pat No. US 5,681,733 PD 28-October-1997, as SEQ ID NO: 4.

Claim 28 is further rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 28 has two interpretations. Claim 28 could recite a polypeptide having the amino acid sequence of SEQ ID NO:4 of US 5,681,733 having (i) substitution of at least one of His36, His105, His110, His139, His152, His225, His234, His241, His424, His469, or His539 with alanine, serine, tyrosine, threonine, or lysine or (ii) any conservative substitutions in SEQ ID NO:4 of US 5,681,733 and having substitution of at least one of His36, His105, His110, His139, His152, His225, His234, His241, His424, His469, or His539 with alanine, serine, tyrosine, threonine, or lysine. Alternatively, Claim 28 could recite (i) a polypeptide having the amino acid sequence of SEQ ID NO:4 of US 5,681,733 or (ii) a polypeptide having the amino acid sequence of SEQ ID NO:4 of US 5,681,733 with any conservative substitution of SEQ ID NO:4 of US 5,681,733 and having substitution of at least one of His36, His105, His110, His139, His152, His225, His234, His241, His424, His469, or His539 with alanine, serine, tyrosine, threonine, or lysine. Appropriate correction is required. Examiner's note: for purposes of examination, it is assumed that Claim 28 recites a polypeptide derived from the amino acid sequence of SEQ ID NO:4 of Su et al, 1997, Pat US5,681,733, having (i) substitution of at least one of His36, His105, His110, His139, His152, His225, His234, His241, His424, His469, or His539 with alanine, serine, tyrosine, threonine, or lysine or (ii) any conservative substitutions of SEQ ID NO:4 of US 5,681,733 and having substitution of at least one of His36, His105, His110, His139, His152, His225, His234, His241, His424, His469, or His539 with alanine, serine, tyrosine, threonine, or lysine.

Claim 28 is also rejected under 35 U.S.C. 112, second paragraph, for reciting "conservative substitutions" which is not defined in the specification. Although very common in the art, the term "conservative substitution" is vague and indefinite. For example, is a Gln/Glu substitution or an Asp/Asn substitution conservative? Are Ser/Tyr and Phe/Tyr conservative substitutions? Another situation that is indefinite is the classification of Gly and Ala; are these small polar residues, similar to Ser, Thr, Gln and Asn, or hydrophobic? Is His basic or hydrophobic? Are linear hydrophobic amino acids similar to aromatic hydrophobic amino acids? Is Cys a small polar amino acid or its own category? Is Tyr a polar amino acid or an aromatic amino acid? Lack of consensus on the answers to these questions causes the term "conservative substitution" to be indefinite. Thus Claim 28 is further rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 23 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 23 recites "A composition, comprising heparinase III... and a targeting molecule..., in a pharmaceutically acceptable carrier". Claim 23 has two interpretations. Claim 23 could mean that the composition comprises, heparinase III, a targeting molecule, and a carrier; a composition comprising three independent substances. Alternatively, Claim 23 could mean that the composition comprises a fusion protein of heparinase III linked to a targeting molecule and a carrier; a composition comprising two independent substances. Clarification is required. Examiner's note: since the specification on page 35 supports the latter interpretation,

for purposes of examination, Claim 23 is read as meaning a composition comprising a fusion protein of heparinase III linked to a targeting molecule and a carrier.

Claim Rejections - 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 28, 32, and 33-35 are rejected under 35 U.S.C. 112, first paragraph. The specification is enabling for the polypeptide set forth by SEQ ID NO: 4 of US5,681,733 and said polypeptide with a His36Ala, His105Ala, His110Ala, His139Ala, His152Ala, His225Ala, His234Ala, His241Ala, His424Ala, His469Ala, or His539Ala mutation (Table 2). However, the specification does not reasonably provide enablement for any heparinase III wherein at least one of His36, His105, His110, His139, His152, His225, His234, His241, His424, His469, or His539 is substituted with alanine, serine, tyrosine, threonine, or lysine. Neither does the specification provide enablement for any heparinase III wherein at least one of His36, His105, His110, His139, His152, His225, His234, His241, His424, His469, or His539 is substituted with alanine, serine, tyrosine, threonine, or lysine and having any number of additional conservative substitutions. Neither does the specification provide enablement for any modified heparinase III having a modified product profile, using any substrate, that is at least 10% different than a native product profile for heparinase III. Neither does the specification provide enablement for any modified heparinase III having, using heparan sulfate as the substrate, a k_{cat} value that is at least 10% different from the k_{cat} value for a native heparinase III. The specification does not enable

any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 28 is so broad as to encompass any heparinase III derived from SEQ ID NO: 4 of US5,681,733 wherein (i) at least one of His36, His105, His110, His139, His152, His225, His234, His241, His424, His469, or His539 is substituted with alanine, serine, tyrosine, threonine, or lysine or (ii) any heparinase III wherein at least one of His36, His105, His110, His139, His152, His225, His234, His241, His424, His469, or His539 is substituted with alanine, serine, tyrosine, threonine, or lysine and having any number of additional conservative substitutions. Claim 32 is so broad as to encompass any substantially purified heparinase III having a modified product profile, using any substrate, that is 10% different from the product profile from native enzyme. Claim 33 is so broad as to encompass any substantially purified heparinase III having a k_{cat} value that is at least 10% different from the k_{cat} value for a native heparinase III using heparan sulfate as the substrate. The scope of each of these claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of proteins broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired heparinase III activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function. However, in this case the disclosure is limited to the amino acid sequence of SEQ ID NO: 4 of US5,681,733 and modified proteins derived from said SEQ ID NO: 4 with a His36Ala, His105Ala, His110Ala,

His139Ala, His152Ala, His225Ala, His234Ala, His241Ala, His424Ala, His469Ala, or His539Ala mutation. While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the results of such modifications are unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of Claim 28 which, encompasses any heparinase III comprising a polypeptide derived from SEQ ID NO: 4 of US5,681,733 wherein (i) at least one of His36, His105, His110, His139, His152, His225, His234, His241, His424, His469, or His539 is substituted with alanine, serine, tyrosine, threonine, or lysine or (ii) any heparinase III having at least one of said substitutions at said histidine residues and having any number of additional conservative substitutions. The specification also does not support the broad scope of the Claim 32 which, encompasses any modified heparinase III having a modified product profile, using any substrate, that is 10% different from the product profile from a native enzyme, or Claim 33 which, encompasses any modified heparinase III having a k_{cat} value that is at least 10% different from the k_{cat} value for a native heparinase, using heparan sulfate as the substrate.

The specification does not support the broad scope of Claims 28, 32, and 33 because, the specification does not establish: (A) regions of the protein's structure which may be modified without effecting the activity of heparinase III; (B) the general tolerance of the activity of heparinase III to modification and extent of such tolerance; (C) a rational and predictable scheme

for modifying any residues with an expectation of obtaining the desired biological function; (D) specific substrates to be used to compare product profiles; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of heparinase III molecules, derived from the protein set forth by SEQ ID NO: 4 of US US5,681,733, with an enormous number of amino acid modifications of said protein. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of the identity of sequences having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Since Claims 34 and 35 are dependent on Claim 28, they are also rejected under 35 U.S.C. 112, first paragraph for the reasons given above.

Claims 28 and 32-35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims are directed to a genus of protein molecules encoding any heparinase III, derived from the protein set forth by SEQ ID NO: 4 of US US5,681,733, having (i) one or more

histidine residues selected His36, His105, His110, His139, His152, His225, His234, His241, His424, His469, or His539 substituted with alanine, serine, tyrosine, threonine, or lysine, (ii) having any number of conservative substitutions and having one or more histidine residues selected His36, His105, His110, His139, His152, His225, His234, His241, His424, His469, or His539 substituted with alanine, serine, tyrosine, threonine, or lysine, (iii) a modified heparinase III having a modified product profile, using any substrate, that is at least 10% different from a native profile, (iv) a modified heparinase III having a Kcat that is at least 10% different from a native Kcat using heparan sulfate as the substrate, (v) a pharmaceutical preparation comprising (i) or (ii), or (vi) an immobilized enzyme preparation comprising (i) or (ii). The specification teaches the structure of only 14 representative species of such proteins. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of having heparinase III activity. Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the sequence being examined was not (1) submitted on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claim 23 is rejected under 35 U.S.C. 102(b) as being anticipated by Bennett et al, 1997. Bennett et al teach the targeting of heparinase III to specific cell types, tissues, or organs using pharmaceutical compositions comprising fusion proteins derived from the enzymes and binding domains from antibodies, growth factors, or adhesion molecules (pg 8, lines 6-10 and 34-36; pg 18, line 25-pg 19, line15; pg 22, lines 12-15;). Therefore, Claim 23 is rejected under 35 U.S.C. 102(b) as being anticipated by Bennett et al, 1997.

Claims 32 and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Lohse et al, 1992. Lohse et al teach a heparinase II which, like heparinase III, uses heparan sulfate as a substrate (Lohse et al; Table III). However, the heparinase II of Lohse et al has, for heparan sulfate, a higher K_m and a lower V_{max} compared to heparinase III (Table III). As described in the specification (page 15, lines 20-22), "...the production of the same types of enzymatic products but in a lesser or greater amount by the modified heparinase, as opposed to the native heparinase, would also constitute a modified product profile". Since the heparinase II of Lohse et al has different kinetic properties, at a set reaction time, the amount of heparan sulfate converted into product would be altered compared to the action of native heparinase III under the same conditions. Claim 32 fails to recite any structural limitation for the modified heparinase III. Thus, the heparinase II of Lohse et al reads on a modified heparinase III that has a product profile that is at least 10% different from the profile derived from native heparinse III. Claim 33 is also rejected under 35 U.S.C. 102(b) as being anticipated by Lohse et al, 1992. For heparan sulfate, the k_{cat} for the heparinse II of Lohse et al is at least 10% different from the k_{cat} of native

heparinase III (Table III). Since Claim 33 fails to recite any structural limitation, the heparinase II of Loshe reads on the modified heparinase III of Claim 33 which has a k_{cat} that is at least 10% different from the k_{cat} of native heparinase III. Therefore, Claims 32 and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Lohse et al, 1992.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 28 is rejected under 35 U.S.C. 103(a) as being unpatentable over Su et al, 1997, Pat. US 5,681,733, in view of Shriver et al, 1998 (In IDS). The teachings of Su et al, 1997 are described above. Su et al, 1997 do not teach mutants of the protein set forth by SEQ ID NO: 4 of Pat. US 5,681,733 which are modified at histidine residues. However, using chemical modification and site-directed mutagenesis, Shriver et al, teach that specific histidine residues of heparinase II are important for enzymatic activity against heparin and heparan sulfate (Abstract; Fig 2 and Table I). Since histidines are important for the activity of heparinase II, a person of ordinary skill in the art would predict that histidine residues are also important for the activity of the heparinase III set forth by SEQ ID NO: 4 of Su et al. Thus, it would have been obvious to a person of ordinary skill in the art use the method of Shriver et al, 1998 to prepare mutants of the heparinase III set forth by SEQ ID NO: 4 of Pat. US 5,681,733. Preparation of His-mutants of the heparinase III of Su et al, 1997 is suggested by the observation that other heparinase His-mutants have altered properties (Shriver et al). Motivation to use the methods of Shriver et al to

prepare His-mutants of the heparinase III, as set forth by SEQ ID NO: 4 of Pat. US 5,681,733, derives from the desire to determine whether histidines do regulate the activity of the heparinase III. The expectation of success is high as site-directed mutagenesis is common in the art (Shriver et al). Therefore, Claim 28 is rejected under 35 U.S.C. 103(a) as being unpatentable over Su et al, 1997 in view of Shriver et al, 1998.

Claim 34 is rejected under 35 U.S.C. 103(a) as being unpatentable over Su et al, 1997 in view of Shriver et al, 1998 and Godavarti et al, 1997 (In IDS). The teachings of Su et al, 1997 and Shriver et al, 1998 are described above wherein it was deemed obvious to make the His-modifed heparinases of Claim 28 based on said teachings. It would also be obvious to a person of ordinary skill in the art to use said His-modified heparinses to prepare a sterile pharmaceutical composition of said heparinases and a carrier. Pharmaceutical preparations comprising sterile formulations of reagents with a pharmaceutically acceptable carrier are well known in the art. For example, Godavarti et al, 1997 teach a pharmaceutical preparation comprising a sterile formulation of heparinase I and a pharmaceutically acceptable carrier (page 35, lines 7-9 and Claim 14) which suggests the preparation of a sterile pharmaceutical formulation comprising the His-modified variants of heparinase III and a pharmaceutically acceptable carrier. Motivation to make said formulations are also provided by Godavarti et al, 1997 who teach the use of formulations containing heparinases for treating subjects in need of depletion of circulating heparin (page 5, lines 4-6). Further motivation is provided by the expectation that one or more His-modified heparinases would have characteristics making their use as a pharmaceutical advantageous. The expectation of success is high as it is very standard in the art to make

pharmaceutical formulations. Therefore, Claim 34 is rejected under 35 U.S.C. 103(a) as being unpatentable over over Su et al, 1997 in view of Shriver et al, 1998 and Godavarti et al, 1997.

Claim 35 is rejected under 35 U.S.C. 103(a) as being unpatentable over Su et al, 1997 in view of Shriver et al, 1998 and Bernstein et al, 1988 (IDS). The teachings of Su et al, 1997 and Shriver et al, 1998 are described above wherein it was deemed obvious to make the His-modifed heparinases of Claim 28 based on said teachings. It would also be obvious to a person of ordinary skill in the art to immobilize said His-modified heparinses to a solid support. Immobilization of proteins to solid supports is common in the art; for example, Bernstein et al, 1988 teach immobilization of a heparinase to a solid support for the purpose of external heparinization of blood followed by enzymatic elimination of the heparin before the blood is returned to the patient. Thus, a person of ordinary skill in the art would be motivated to prepare a product wherein His-modified heparinses are immobilize to a solid support. Said product could be used in a procedure wherein blood is heparinized and then enzymatically deheparinized externally which, is a means to reduce the risk of hemorrhagic complication (Berstein et al). Further motivation is provided by the expectation that one or more His-modified heparinases would have characteristics making their use advantageous in said procedure. The expectation of success is high because, attachment of proteins to solid supports is common in the art (Bernstein et al, 1988). Therefore, Claim 35 is rejected under 35 U.S.C. 103(a) as being unpatentable over Su et al, 1997 in view of Shriver et al, 1998 and Bernstein et al, 1988 (IDS).

Claim Rejections - 35 USC § 101

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible

harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 32 and 33 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claim 1 of U.S. Patent No. 5,389,539 (Sasisekharan et al, 1995). An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not is patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other. Both Claim 32 and Claim 1 of 5,389,539 recite a heparinase that uses heparan sulfate as a substrate (see Table III; heparinase II). Claim 32 of this application recites a modified heparinase III having a product profile that is at least 10% different compared to native heparinase III. Claim 32 fails to recite any structural limitation or pH optimum for the modified heparinase III. Claim 1 of U.S. Patent No. 5,389,539 is directed to a heparinase that has a higher K_m and a lower V_{max} compared to heparinase III (Table III: heparinase II). Since the heparinase II of 5,389,539 has different kinetic properties, the amount of heparan sulfate converted into product would be altered compared to the action of native heparinase III under the same conditions. Thus, the heparinase II of 5,389,539 reads on a modified heparinase III that has a product profile which is at least 10% different from the profile

derived from native heparinse III and is encompassed by Claim 33 of this application. Similarly, Claim 33 and Claim 1 of U.S. Patent No. 5,389,539 are both directed to a heparinase that uses heparan sulfate as a substrate and has a modified K_{cat} value that is at least 10% different from the K_{cat} value for native heparinase III (Table III: heparinase II). Thus, Claim 1 of U.S. Patent No. 5,389,539 is encompassed by Claim 33 of this application. Therefore, Claims 32 and 33 are rejected under obviousness-type double patenting as being unpatentable over Claim 1 of U.S. Patent No. 5,389,539 (Sasisekharan et al, 1995).

Claim 27 is objected to for being dependent on a rejected claim. However, Claim 27 would be allowable if rewritten in independent form with all the limitations of Claim 23 and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 703-305-1696. The examiner can normally be reached on M-F; 8:30-5 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 703-308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Sheridan L. Swope, Ph.D.

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